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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/980,403	04/15/2002	Donald Gullberg	000510-010	3147

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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 10/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/980,403	GULLBERG, DONALD	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-149* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,11,13,14,20,22-25,28,94,106,113,115,116,119,121-124,126,146 and 149* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/28/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 2-10, 12, 15-19, 21,26, 27, 29-93, 95--105, 107-112, 114, 117, 118, 120, 125, 127-145, 147-148.

DETAILED ACTION

1. Claims 1-149 are pending.

2. Applicant's election with traverse of Group I, claims 1, 11, 13, 14, 20, 22-25, 28, 94, 106, 113, 115, 116, 119, 121-124, 126, 146 and 149 drawn to a recombinant or isolated integrin subunit α11 having the amino acid sequence encoded by SEQ ID NO: 1 and homologues and fragments thereof and a vaccine filed on 9/13/04, is acknowledged.

Applicant's traversal is on the grounds that the Examiner has not establish that there would be an undue burden to examine all of the groups together in the same application. This is not found persuasive because Applicant's inventions do not contribute a special technical feature when viewed over the prior art they do not have a single general inventive concept and so lack unity of invention as set forth in the previous Office Action. Further, a prior art search also requires a literature search. It is an undue burden for the examiner to search more than one invention.

The requirement is still deemed proper and is therefore made FINAL

3. Claims 2-10, 12, 15-19, 21,26, 27, 29-93, 95-105, 107-112, 114, 117, 118, 120, 125, 127-145, 147-148. are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

4. Claims 1, 11, 13, 14, 20, 22-25, 28, 94, 106, 113, 115, 116, 119, 121-124, 126, 146 and 149 are under examination as they read on a recombinant or isolated integrin subunit α11 having the amino acid sequence encoded by SEQ ID NO: 1 and homologues and fragments thereof and a vaccine.

5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

One sequence appears on page 9, line 12, two sequences appear on page 21, line 14, and a sequence appears in claims 23, 122, and 149 fail to comply with the sequence rule.

6. The specification is objected to under 37 CFR 1.821(d) for failing to provide a sequence identifier for each individual sequence. Figure 2, on page 33, has describe nucleotide and deduced amino acid sequence of the human integrin α11 chain sequences murine and human that each must have a sequence identifier. Correction is required.

7. The specification on page 1 should be amended to reflect the relationship between PCT/SE00/01135 and Sweden 9902056-2 and instant application. 37 CFR 1.78(a) requires that benefit claims under 35 U.S.C. 120 or 119(e) to be submitted in the first sentence of the specification or in an ADS. If the applicant submit a benefit claim under 120 in the oath or dec., the benefit claim would not be proper. The applicant is still required to submit the benefit claim in the specification or ADS.

8. It is improper to recite "binding sites" in claims 11, 28, 113, 119, 126, line 1, as the claims should recite the singular form. It is suggested that the word be changed to "A binding site".

9. Claims 23, 122, and 149 are objected to under 37 CRD 1.821(d) because it lacks a amino acid sequence identifier.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 1, 11, 13, 14, 20, 22-25, 28, 94, 106, 113, 115, 116, 119, 121-124, 126, 146 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. The recitation of "the amino acid sequence shown I SEQ ID No.1" in claims 1, 13, 22, 24, 106, 121, 123-124 are indefinite because SEQ ID NO: 1 is a nucleic acid sequence and limited to its nucleic acid components. Applicants have failed to point out how an amino acid would have a nucleic acid sequence of SEQ ID NO: 1.

B. The "chosen from the group comprising" recited in claims 11, 22 and 28 is indefinite for being in improper Markush format. The Office recommends the use of the phrase "selected from the group consisting of ..." with the use of the conjunction "and" rather than "or" in listing the species. See MPEP 706.03(Y).

C. The "fragments thereof" recited in claims 1, 11, 13, 20, 28, 94, , 113, 119, and 126 are indefinite because it is unclear whether the phrase refers to the SEQ ID NO.1 or the homologues.

D. Claims 24, 25, 123, 124 is indefinite for reciting "from about 4-30 amino acid" No. It is unclear how many amino acids constitute "about". One of skill in the art would not know if applicant meant ± 4 amino acid, as many as ±11 amino acids, or even more.

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is

most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 1, 11, 13, 14, 20, 22-25, 28, 94, 113, 115, 116, 119, 121-124, 126, 146 and 149 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling an isolated integrin subunit α11 having the amino acid sequence of SEQ ID NO: 2 and a composition thereof; a heterodimer comprising α11β1; a fragment consisting of the amino acid sequence KLGFFRSARRRREPGLDPTPKVLE, the extracellular domain consisting of amino acids 804-826 of SEQ ID NO:2, the I-domain consisting of amino acid 159 to 355 of SEQ ID NO:2 and a composition thereof, does not reasonably provide **enablement** for a recombinant or isolated integrin subunit α11 "having" the amino acid fragments of SEQ ID No. 1 or "homologues or fragments thereof" in claim 1, binding sites of the amino acid sequence of the integrin subunit α11, or of hmologues and fragments thereof, wherein said binding sites having the capability of binding specifically to entities chosen from the groups comprising proteins, peptides, carbohydrates, lipids, natural integrin binding ligands, polyclonal and monoclonal antibodies and fragments thereof in claims 11, 14, 28, 113, 119, 126, a recombinant or isolated integrin heterodimer comprising a subunit α11 and any subunit β in claims 115, the subunit a having the amino acid sequence shown in SEQ ID NO: 1 or "homologues or fragments thereof" in claim 13, wherein the subunit β is β1 in claim 14; a fragment of an integrin subunit α11, which integrin subunit α11 has the amino acid sequence shown in SEQ ID NO:1, said fragment being any "peptide" chosen from the group comprising peptides of the cytoplasmic domain, the I-domains and the extracellular extension region in claims 22, 121 said fragment being a peptide from the cytoplasmic domain "having" the amino acid sequence LGFFRSARRRREPGLDPTPKVLE in claims 23, 122 and 149, which is a peptide "having" the amino acid sequence of the extracellular domain, from about amino acid No. 804 to about amino acid No. 826 of SEQ ID NO:1 in claims 24, 123, which is a peptide "having" the amino acid sequence of the I-domain, from about amino acid No 159 to about amino acid No.355 of SEQ ID NO:1 in claims 25, 124, a "vaccine" comprising as an active ingredient "at least one member of the group consisting of an integrin heterodimer", which heterodimer comprises a subunit α11 and a subunit b, or the subunit α11 thereof, and homologues or fragments of said integrin or subunit α11, and a polynucleotide and oligonucleotide coding for said integrin subunit α11 in claims 94 and 146. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.

The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation.

Claims 11, 20, 28, 113, 119, and 126 recite binding sites of the amino acid sequence of the integrin subunit α11, however it is recognized in the art that alterations in protein structure lead to alterations in bindings affinity proportional to the magnitude of the alteration (Miller et al, abstract, lines 2-4). Further, Kuntz teaches that as little as 2% of compounds predicted to inhibit specific enzymztic or receptor systems actually shown inhibition in the micromolar range (page

1080, 3rd col.). The claims encompass alterations in protein folding because claims permit deviation from the amino acid sequence of SEQ ID NO: 2. Neither is antibody binding seen as sufficiently limiting since an antibody epitope may be as small as 6-15 shared amino acid residues (e.g., Lerner Nature 1982; 299:592-596, see page 595-596) and places no limitations on the function of the protein containing the polypeptide sequence recognized. Finally, neither the art nor the specification recognize that α11 integrin subunit has binding sites for carbohydrates or lipids. It would be reasonable to conclude that alterations in protein folding would lead to a large alteration in binding affinity.

Claims 1, 11, 13 and 14 recite "homologues" of SEQ ID NO: 1, however, Skolnick et al. (Trends in Biotech. 2000; 18(1):34-39) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Similarly, Attwood (Science 2000; 290:471-473) teaches that "[i]t is presumptuous to make functional assignments merely on the basis of some degree of similarity between sequences. Thus it is unpredictable if any functional activity will be shared by two polypeptides having less than 100% identity over the full length of their sequences.

Claims 13, 115, 146 recite that the integrin heterodimer comprising any "subunit β", however, the specification on page 24, lines 14-35 discloses that an antibody which was raised to the cytoplasmic tail of the integrin α11 chain immuoprecipitated a 145 KDa α11 band associated with a 115 KDa β1 band in SDS-PAGE under non-reducing conditions. Further, the specification on page 25, line 3-11 discloses that α11 is associated with the β1 subunit. Besides β1, the specification falls to provide α11 heterodimer comprising any β subunit.

The terms "comprising" and "having" in claims 1, 13, 22-25, 121, 122-124 and 149 is open ended and extend the fragment peptides to include additional on either or both sides of the cytoplasmic domain, I-domain, the extracellular extension region or the specific peptide other than KLGFFRSARRRREPGLDPTPKVLE, aa804-826 and aa159-355. It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions can result in substantially different biological activities. Because of the lack of sufficient guidance and predictability in determining which modifications would lead to the collagen type I binding and that the relationship between the peptide and its activity was not well understood. It would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of fragments of integrin subunit α11 that binds collagen type I. Without sufficient guidance, the changes which can be made in the structure of "fragment" and still provide collagen type I binding activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Also, at issue is whether or not the claimed composition would function as vaccine. In view of the absence of a specific and detailed description in Applicant's specification of how to effectively use the vaccine as claimed, and absence of working examples providing evidence

which is reasonably predictive that the claimed vaccine are effective for in vivo use, and the lack of predictability in the art at the time the invention was made, an undue amount of experimentation would be required to practice the claimed pharmaceutical composition with a reasonable expectation of success. If the use disclosed is of such nature that the art is unaware of successful treatments with chemically analogous compounds, a more complete statement of how to use must be supplied.

The lack of any working examples is exacerbated because the invention is in a highly unpredictable art-prevention/vaccination- and while the level of skill of in the art may be high, the state of the prior art is that it is in fact unknown and untested what are the underlying adhesion molecule and physiologic bases of the therapeutic effects of α11 integrin subunit in the prevention/vaccination.

14. Claims 1, 11, 13, 14, 20, 22-25, 28, 94, 113, 115, 116, 119, 121-124, 126, 146 and 149 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession an isolated integrin subunit α11 having the amino acid sequence of SEQ ID NO: 2 and a composition thereof; a heterodimer comprising α11β1; a fragment consisting of the amino acid sequence KLGFFRSARRRREPGLDPTPKVLE, the extracellular domain consisting of amino acids 804-826 of SEQ ID NO:2, the I-domain consisting of amino acid 159 to 355 of SEQ ID NO:2 and a composition thereof.

Applicant is not in possession of any recombinant or isolated integrin subunit α11 "having" the amino acid fragments of SEQ ID No. 1 or "homologues or fragments thereof" in claim 1, binding sites of the amino acid sequence of the integrin subunit α11, or of hmologues and fragments thereof, wherein said binding sites having the capability of binding specifically to entities chosen from the groups comprising proteins, peptides, carbohydrates, lipids, natural integrin binding ligands, polyclonal and monoclonal antibodies and fragments thereof in claims 11, 14, 28, 113, 119, 126, a recombinant or isolated integrin heterodimer comprising a subunit α11 and any subunit β in claims 115, the subunit a having the amino acid sequence shown in SEQ ID NO: 1 or "homologues or fragments thereof" in claim 13, wherein the subunit β is β1 in claim 14; a fragment of an integrin subunit α11, which integrin subunit α11 has the amino acid sequence shown in SEQ ID NO:1, said fragment being any "peptide" chosen from the group comprising peptides of the cytoplasmic domain, the I-domains and the extracellular extension region in claims 22, 121 said fragment being a peptide from the cytoplasmic domain "having" the amino acid sequence LGFFRSARRRREPGLDPTPKVLE in claims 23, 122 and 149, which is a peptide "having" the amino acid sequence of the extracellular domain, from about amino acid No. 804 to about amino acid No. 826 of SEQ ID NO:1 in claims 24, 123, which is a peptide "having" the amino acid sequence of the I-domain, from about amino acid No 159 to about amino acid No.355 of SEQ ID NO:1 in claims 25, 124, a "vaccine" comprising as an active ingredient "at least one member of the group consisting of an integrin heterodimer", which heterodimer comprises a

subunit α11 and a subunit b, or the subunit α11 thereof, and homologues or fragments of said integrin or subunit α11, and a polynucleotide and oligonucleotide coding for said integrin subunit α11 in claims 94 and 146

Neither the exemplary embodiments nor the specification's general method appears to describe structural features, in structural terms, that are common to the genus. That is, the specification provides neither a representative number of species (homologues, fragments, binding sites, heterodimers) to describe the claimed genus, nor does it provide a description of structural features that are common to species (homologues, fragments, binding sites, heterodimers). Tthe specification provides no structural description of homologues, fragments, binding sites, heterodimers other than ones specifically exemplified; in essence, the specification simply directs those skilled in the art to go figure out for themselves what the claimed homologues, fragments, binding sites, heterodimers looks like. The specification's disclosure is inadequate to describe the claimed genus of homologues, fragments, binding sites, heterodimers.

Applicant has disclosed only amino acid of SEQ ID NO: 2 that associates with β1 subunit; and the specific fragment consisting of the amino acid sequence KLGFFRSARRRREPGLDPTPKVLE, the extracellular domain consisting of amino acids 804-826 of SEQ ID NO:2, the I-domain consisting of amino acid 159 to 355 of SEQ ID NO:2 therefore, the skilled artisan cannot envision all the contemplated amino acid sequence possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claims 1, 13, 14, 20, 94, 106, 115, 116 and 146 are rejected under 35 U.S.C. 102(b) as being anticipated by Gullberg *et al* (Dev. Dyn. 204:57-65, 1995) (IDS Ref. No. C2), as is evidenced by Velling *et al* (IDS Ref. No. C5).

Gullberg *et al* teach an isolated integrin subunit αmt obtained from G6 myoblasts and myotubes. Gullberg *et al* teach that αmt is induced upon myogenic differentiation (see abstract). Gullber et al teaches that under non-reducing conditions β1 associated protein migrated as 145 kD, wherein under reducing conditions, β1 integrin associated protein migrated in SDS-PAGE as a 155 kD protein (see abstract in particular). Gullberg *et al* teach that αmtβ1 heterodimer (see page 60, 2nd col., 2nd ¶ in particular). While the Gullberg *et al* teachings may be silent as to the "SEQ ID NO: 2" per se; the product is the same as the claimed product. As is evidenced by Velling *et al* that α11 is identical with αmt (see page 25740, 2nd col., end of the 1st ¶ in particular). Therefore "SEQ ID NO:2" is considered inherent properties.

Claims 94, and 146 are included because the claims recite the same products and the intended uses do not carry patentable weight per se and the claims read on the active or essential ingredients of α11.

The reference teachings anticipate the claimed invention.

17. Claims 11, 20, 22, 28, 94, 113, 119, 121 are 126 are rejected under 35 U.S.C. 102(b) as being anticipated by 5,686,059 (of record, 892 Ref).

The `059 patent teaches a CBS1 motif included in the rat VLA-1 integrin molecule consisting of DIVIVLDGS fragment (referenced SEQ ID NO: 34, in particular) that corresponds to amino acid residues 164-172 of claimed amino acid sequence encoded by SEQ ID NO: 1 (see col. 4, lines 10-11 in particular). The referenced fragment would bind proteins, peptides natural integrin binding ligands, and antibodies. Further, the referenced fragment is a peptide of the I-domain.

Claim 94 is included because it recites the same products and the intended uses do not carry patentable weight per se and the claims read on the active or essential ingredients of fragments.

The reference teachings anticipate the claimed invention.

18. No claim is allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maher Haddad, Ph.D.
Patent Examiner
Technology Center 1600
September 30, 2004

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Application No.

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES 09/980,463

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 CFR 1.821 - 1.825 for the following reason(s):

☐ 1. This application clearly fails to comply with the requirements of 37 CFR 1.821 - 1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 CFR 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 CFR 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 CFR 1.822 and/or 1.823, as indicated on the attached copy of the marked-up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A substitute computer readable form must be submitted as required by 37 CFR 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 CFR 1.821(e).

☐ 7.

Other: _____

Applicant must provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing"

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d)

For questions regarding compliance with these requirements, please contact:

For Rules Interpretation, call (703) 308-1123
For CRF submission help, call (703) 308-4212
For PatentIn software help, call (703) 557-0400

Please return a copy of this notice with your response.